IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Examiner: G. Ewoldt
Steinunn Baekkeskov *et al.*	Art Unit: 1644
Application No.: 08/838,486	SECOND DECLARATION OF STEINUNN BAEKKESKOV UNDER 37 CFR §1.132
Filed: April 7, 1997	
For: IMPROVED METHODS FOR THE DIAGNOSIS AND TREATMENT OF DIABETES	

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Steinunn Baekkeskov, state as follows:

1. I have previously submitted a declaration in these proceedings. My experience and qualifications are summarized in that declaration.

2. In the present declaration, I address two additional points raised in the final office action.

3. As discussed in my previous declaration and an accompanying Press Release, a phase II clinical trial is being conducted to test treatment of GAD on patients with a subtype of type II diabetes termed LADA (Latent Autoimmune Diabetes in Adults). A 6-month report on the trial provided evidence that administration of 20 micrograms GAD was safe and provided statistically significant evidence of efficacy over placebo ($p=0.0008$). Recently the 18-month data from the Phase II studies were released (Immunology of Diabetes Society's 7th Congress, March 29-31, 2004, Cambridge, England). The report showed that the positive effect on insulin production achieved six months after treatment still remains eighteen months after treatment and provided evidence that this effect is mediated by induction of regulatory T-cells (CD4+CD25+) (see enclosed press release of

March 29, 2004). I understand the Examiner disregards the evidence obtained 6 months after treatment on the basis that the trial was conducted on patients suffering from a "related pathology of non-autoimmune origin" (final office action at p. 4). This position is incorrect.

4. Patients with LADA subtype of type II diabetes are patients whose initial presentation of disease masquerades as type 2 diabetes because of its late onset, but whose underlying pathology including presence of autoimmune attack on GAD, is characteristic of type I diabetes (also known as IDDM) (see attached excerpt from DiabetesMonitor.com). Thus, the LADA subtype, as indicated by its name, Late Autoimmune Diabetes in Adults, is generally recognized as being a form of type I diabetes with a late onset. These patients undergo the same autoimmune destruction of beta pancreatic cells as other Type 1 patients, and are expected to benefit from immunotolerance by GAD therapy as other Type 1 patients. The reasons for starting prophylactic therapy in this group of patients rather than in asymptomatic children include that LADA patients regularly receive medical care, and that the clinical benefits can be detected more quickly (see attached press release). Both of these factors facilitate conducting a clinical trial

5. Because LADA patients undergo the same autoimmune destruction of beta pancreatic cells as other Type 1 patient, in my opinion, the results obtained in the phase II trial for treatment of LADA patients with GAD would also be expected for other Type 1 diabetes patients treated with GAD.

6. I understand that the above captioned application has claims to a composition for parenteral use containing lower molecular molecular weight GAD at a purity of at least 99% w/w.

7. In my opinion, it would have been extremely difficult to purify the 64 kDa antigen to the extent recited in the amended claims (at least 99 % pure) from the natural source of β-

pancreatic islet cells at the priority date of the application. This difficulty is based on the following facts.

8. One difficulty limiting purification was the small quantities of pancreatic islet cells available and the fact that of this small amount of material, that 64 kDa antigen was known to constitute less than 0.1% of total islet proteins (Baekkeskov et al., *Diabetes* 38, 1133-1141 (1989)). In fact, I spent a year of my scientific life (1984-85) attempting to purify minute amounts of radioactive protein from 26 human islet cell preparation, but did not obtain sufficient quantities to obtain a sequence, even though I collaborated with Drs. Hunkapiller and Hood, who had the best microsequencing facility in the world at the time and had pioneered the microsequencing technique. I am also aware of several futile attempts to purify the protein from islet cells by other groups.

9. A second difficulty was the absence of a simple and specific assay by which the yield of antigen could be assessed at each step in a purification procedure. The yield could be assessed only by immunoprecipitation of radioactive proteins using autoantibody positive human IDDM patient sera, followed by gel analysis and autoradiography. No other technique was sensitive enough to detect the minute amounts of protein obtained from islets. As well as being tedious, this assay procedure would have consumed much of the sample sought to be purified.

10. A third difficulty was the need to achieve purification without impairing the conformation of the 64 kDa antigen required for subsequent use of the antigen in a pharmaceutical composition, because the human patient IDDM sera only reacted with conformational epitopes. The need to preserve conformation would have restricted the choice of solvents from the repertoire generally employed in protein purification (e.g., use of SDS or organic solvents would denature the antigen).

11. A fourth difficulty was the heterogeneous nature of the 64 kDa antigen. As noted in the background section of the present application, the 64 kDa antigen exists in a number of forms differing with respect to subcellular location, hydrophobicity and charge/mobility on SDS-gels (*see* specification at p. 4). Thus, different conditions might have been required to have attempted to purify each of the different forms. Without attempting to preserve each of the different forms throughout purification, there would have been no assurance that what was being purified was the appropriate form of the 64 kDa antigen for inclusion in a pharmaceutical composition to treat IDDM.

12. For these reasons, I do not believe that I or other skilled practitioners would have succeeded in obtaining the 64 kDa in at least 99% pure form suitable for use in a pharmaceutical composition without the insight that the 64 kDa autoantigen was GAD, which allowed purification from more abundant sources such as brain or a recombinant cellular expression system.

(13) I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

Steinunn Baekkeskov

Date 4/27/04

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DIAMYD MEDICAL

Press Release

Stockholm, March 29, 2004

Diamyd reports increased long-term effect in diabetes pharmaceutical and carries out guaranteed new share issue

· 18-month data from the Phase II studies with Diamyd™ for the treatment of autoimmune diabetes shows that the positive effects achieved after six months remain and are increased. Furthermore, the mechanism, i.e. the underlying reason for the effect of Diamyd™, has been identified.

· These positive results are going to be of great importance in creating advantageous conditions in the Company's ongoing process of finalizing a licensing agreement with an industrial partner.

· To improve the Company's position even further in the ongoing discussions on licensing with a third party and to make continued development of the Company's patented GAD platform possible, on March 26, 2004 the Board decided to carry out a new share issue.

· If fully subscribed the Company will receive approximately SEK 92 million.

· The new share issue, conditional on the approval of an extraordinary general meeting on April 27, 2004, has been completely guaranteed by a consortium consisting of both existing shareholders and new institutional shareholders.

· The Board also intends to request authorization from the general meeting to accept over-subscription from the shareholders equivalent to 20% of the outstanding number of shares after the rights issue described above.

Long-term results from Diamyd Medical's Phase II study

At the IDS7 diabetes congress in Cambridge, England on March 29-31 2004, significant progress from the Company's Phase II studies with the diabetes treatment Diamyd™ is being presented.

Diamyd™ provides long-term effect

An earlier six-month report from the study (Lernmark, ADA, June 2003) showed that insulin production, normalized for glucose concentration, increased significantly in diabetes patients who were treated with 20 µg Diamyd™ compared with a placebo ($p=0.0008$). The results being presented at Cambridge show both the mechanism of the treatment's function and that the increased insulin production still remains at the improved level 18 months after the treatment. This data indicates that the autoimmune attack against the patient's insulin-producing cells has either been kept in check or stopped.

Evaluation of further parameters that verify the effect of the pharmaceutical preparation
Aiming to further verify the effect of the treatment, the Company has evaluated the changes in the average blood sugar levels (HbA1c). 18 months after the treatment with 20 mg Diamyd™, the results show a statistically significant improvement compared with a placebo ($p=0.009$). The change between the 20 mg dose group and the placebo group was about 20%, which is very positive as only a change of 5% is considered to have a significant importance for HbA1c.

The mechanism of the treatment has been identified and proved

The immunological mechanism underlying Diamyd™ treatment has been proved. The number of regulatory T-cells, measured as the T-cell quotient CD4+CD25+/CD4+CD25-, increased after 6 months in patients treated with Diamyd™ who showed increased insulin production (r=0.56; p=0.001). GAD specific regulatory T-cells are considered to cause a lowering of the autoimmune inflammation in the insulin-producing cells of the pancreas.

Carl-David Agardh, professor of diabetes research at Lund University, Sweden and head physician at the University Hospital, UMAS, in Malmö, Sweden and who is in charge of the study, says:

"The 18-month results confirm and strengthen the results obtained after 6 months. This is very promising. Patients in which we succeeded in maintaining their own production of insulin are expected to experience significantly reduced complications at a later date."

Target groups for Diamyd™ – autoimmune diabetes

There are various types of diabetes. Type 1 diabetes, insulin-dependent diabetes, is the type that normally appears in young people and that requires daily injections of insulin. Type 1 diabetes is an autoimmune disease, i.e. the immune system attacks and kills the body's own insulin-producing beta-cells. When about 85% of all the insulin-producing cells have been destroyed the remaining beta-cells cannot produce sufficient insulin and the patient is obliged to take daily insulin injections.

With type 2 diabetes the patient normally retains the ability to produce insulin. However the insulin has lost some of its potency – the insulin sensitivity has been reduced – which results in elevated blood sugar levels. These patients are often treated with pharmaceutical preparations in the form of tablets for their insulin sensitivity.

About 10% of all diabetics have a form of the disease that, simply put, is seen to lie between type 1 and type 2 diabetes. This form of the disease is called Latent Autoimmune Diabetes in Adults, LADA, and is a slowly progressive form of autoimmune diabetes that does not often appear before adulthood. LADA patients are identified as being diabetics who do not as yet need to take insulin injections but who have antibodies against GAD. This means that these patients have an autoimmune form of diabetes that results in their beta-cells successively being destroyed and that they thereby become dependent on insulin injections within a year or two.

"The first application for Diamyd™ is seen to be LADA patients" says Anders Essen-Möller, CEO of Diamyd Medical. "It is this group that has participated in the Phase II study. There are several reasons for this. The patients are adults, they already have diabetes and they regularly receive medical care. It is known that their beta-cells will be destroyed so that they will become dependent on insulin injections but even so they have more remaining beta-cells than type 1 patients. The sooner the treatment is started, the greater the chance of achieving appositive result. Furthermore, the LADA group is large when seen as a market and more than justifies the development of the pharmaceutical preparation from an economic point of view."

The next application is the treatment of new onset type 1 diabetes. The aim is to stop the autoimmune process that results in the destruction of the patient's remaining beta-cells with two injections of Diamyd™. Our long-term objective is to vaccinate children to prevent the disease.

"With the new, positive results and the guaranteed capital issue we can now lift the Company to a new level where we can evaluate new applications for our GAD technology at the same time as we can continue negotiations for licensing with a stronger capital base."

From pharmaceutical to vaccine

The Company's first applications with Diamyd™ is seen, as mentioned above, to be a treatment for LADA patients and also later for new onset type 1 diabetes patients so that they can retain their own insulin production. The long-term aim, however, is to develop a vaccine for whole groups of the population. "Major screening studies are underway around the world, among them all newly born babies in the Swedish region of Skåne, to try and identify those who run the risk of developing type 1 diabetes," says Åke Lernmark, Professor of Medicine at the University of Washington in Seattle, US. "Now we have found a possible mechanism for auto-gene treatment of LADA patients – we have shown that regulatory T-lymphocytes increase in patients in which the production of insulin increases – so I hope in the future to be able to treat children at risk at an early stage and to try and eliminate type 1 diabetes in children and young people.

Professor Lernmark is also Professor of Experimental Diabetes at Lund University, Department of Endocrinology at the University Hospital in Malmö. At an early stage Prof. Lernmark focused his attention on diabetes and the antigen that later proved to be GAD. He was one of the first to show the presence of antibodies against GAD in insulin-dependent diabetes. Prof. Lernmark has been a member of Diamyd Medical's Scientific and Medical Council since 1996.

Daniel Kaufman, Professor at the Department for Molecular and Medical Pharmacology at UCLA, showed in 1993 that giving GAD to mice that normally develop insulin-dependent diabetes prevented the outbreak of the disease. This research formed the basis of UCLA's patent portfolio around GAD and the fundamental patent was granted in the US as late as January 2004. The patent portfolio, for which Diamyd Medical has an exclusive license, therefore provides protection until 2021, According to Prof. Kaufman, who is a member of Diamyd Medical's Scientific and Medical Council: *"The vaccine to prevent type 1 diabetes arose from experiments at UCLA with diabetes-prone mice that were protected from developing the disease by vaccinating them with a protein from the insulin producing cells called GAD. It's tremendously satisfying to see our work at UCLA go from the lab to a clinical application with the potential to help so many people"*

Other applications for the Company's GAD technology platform

At present Diamyd Medical is developing the pharmaceutical based on the GAD65 (glutamic acid decarboxylase) technology platform for diabetes. The Company intends to evaluate the opportunities for R&D in the following areas:

Obesity

The GAD gene has been identified as the candidate gene for obesity. The Company intends to investigate the possibilities of developing a treatment for obesity based on GAD65.

Parkinson's Disease

GAD therapy is being investigated by another organization for treating Parkinson's disease. Diamyd Medical intends to issue a license for the GAD-based therapy for Parkinson's disease.

SMS

Antibodies against GAD have been found in patients with the rare movement inhibitory disease SMS. There is a possibility for applying for an Orphan Drug Status for the treatment of SMS. Diamyd Medical has devised a preclinical plan as a basis for carrying out small-scale clinical trials.

New Share Issue

The Board for Diamyd Medical AB (publ) has decided on a new share issue of a maximum of about SEK 92 million, equivalent to a maximum of 2,314,288 shares or the higher amount and number of shares (maximum 71,277 series B shares) that can follow because of subscription of shares supported by outstanding option rights. The issue price has been fixed at SEK 40 per share. Each even numbered share of series A and B gives the right to subscribe to a new share of series B. The rights issue decision is conditional on the approval of an extraordinary general meeting to be held on April 27, 2004 in Stockholm. In the event of the rights issue being fully subscribed, the Board also intends to request authorization from the extraordinary general meeting to carry out another new share issue of at most 1,431,327 shares, equivalent to 20% of the outstanding number of shares after the rights issue described above, at an issue price of SEK 40 per share.

The issue in its entirety has been guaranteed by a declaration of intent from a consortium consisting of both existing shareholders and a number of new institutional owners. Existing shareholders shall have preferential subscription rights.

This new share issue strengthens the Company's position as a credible and long-term partner for industrial players. At the same time the Company's position is strengthened in ongoing negotiations for the issuing of a license for Diamyd™. Furthermore, the emission gives the Company the possibility of further developing the Company's GAD platform within the framework of the strong patent portfolio.

The positive results from the Phase II study provide the possibility of evaluating and developing new, potential pharmaceutical candidates, not only for the treatment of diabetes but also for other metabolic and neurological diseases.

Schedule

Extraordinary general meeting	April 27, 2004
Final day for share trading with right to participate in the new share issue	April 29, 2004
Record day for right to participate in the new share issue	May 4, 2004
Trade with subscription rights	May 7 - 25, 2004
Subscription period	May 7 - 28, 2004

A prospectus is expected to be available during the week starting May 3.

ABG Sundal Collier AB is advisor to the Company in the capital rights issue in question.

Stockholm March 26, 2004
Diamyd Medical AB
The Board

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LADA

Jump to a new section

Latent Autoimmune Diabetes in Adults is a form of type 1 diabetes which is diagnosed in individuals who are older than the usual age of onset of type 1 diabetes. It is frequently confused with type 2 diabetes.

Latent Autoimmune Diabetes in Adults (LADA) is a form of *autoimmune* diabetes (*type 1A* diabetes) which is diagnosed in individuals who are older than the usual age of onset of type 1 diabetes (that is, over 30 years of age at diagnosis). Alternate terms that have been used for "LADA" include Late-onset Autoimmune Diabetes of Adulthood, "Slow Onset Type 1" diabetes, and sometimes also "Type 1.5 [Type one-and-a-half]" diabetes.

Often, patients with LADA are mistakenly thought to have *type 2* diabetes, based on their age at the time of diagnosis. Such misdiagnosis is easy to make when the person is older, and initially responds to treatment with diabetes pills. It is now thought that perhaps twenty percent of patients with apparent Type 2 diabetes really have LADA.

Patients with LADA do not have *insulin resistance*, as do people with Type 2. Also, positive antibody tests would help make the diagnosis of LADA in a person who might be suspected of having either LADA or Type 2.

Some diabetes specialists feel that once LADA is diagnosed, it is important to promptly start the patient on insulin therapy (rather than using *sulfonylureas* or other diabetes pills), but it is unclear whether early treatment with insulin is beneficial for the remaining *beta cells*.

Drug therapy to preserve insulin function in patients with LADA is being investigated.

Characteristics of LADA

- Adult age at diagnosis (usually over 25 years of age)
- Initial presentation masquerades as non-obese type 2 diabetes (does not present as *diabetic ketoacidosis*)
- Initially can be controlled with meal planning with or without diabetes pills
- Insulin dependency gradually occurs, frequently within months
- Positive *antibodies*
- Low *C-peptide* levels.
- Unlikely to have a family history of type 2 diabetes.

Also see:

- *Type 1.5 Diabetes*
- *Latent Autoimmune Diabetes in Adults* (PDF file)
- *Autoimmune diabetes not requiring insulin at diagnosis (latent autoimmune diabetes of the adult): definition, characterization, and potential prevention.* (Abstract at PubMed)
- *Progress in the characterization of slowly progressive autoimmune diabetes in adult patients (LADA or type 1.5 diabetes).* (Abstract at PubMed)
- *New Drug Arrests Progression of Type 1 Diabetes*

Revised March 5, 2003